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Effective treatment of an extensive recurrent breast cancer which was refractory to multimodal therapy by multiple applications of electrochemotherapy

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ABSTRACT

The application of combined chemotherapy and cancer cell permeabilising electric pulses (electrochemotherapy) has been demonstrated here to be clinically effective in the treatment and control of extensive breast cancer. In this case study the application has proven to be successful in the palliative treatment of a patient with recurrent breast wall cancer nodules, where conventional modes of treatment were ineffective in reducing or eliminating the cancer. This novel therapy offers a new surgical approach for the treatment and elimination of previously refractory cancers, improving the survival and quality of life options available to cancer patients.

1. Introduction

Local recurrences which are recalcitrant to multimodal therapies occur in approximately 6% of patients who are treated for breast cancer.[1] Tumour recurrences are often multiple and progress rapidly resulting in painful skin ulceration, malodorous discharge and bleeding. Such problems are difficult to manage clinically. In this context surgical resection and chest wall reconstruction requires prolonged convalescence, is prone to the complications of wound failure and to further local tumour recurrences and is rarely applicable to large-scale disease particularly if there are systemic metastases. On the other hand palliative measures are problematic where extensive painful discharging wounds require frequent applications of dressings. A major problem is the severe psychological distress for the patient who is witness to the disease progression and evident therapeutic failure. We report the significant benefit of electrochemotherapy to the management of an extensive chest wall recurrence of a breast cancer, after multimodal therapy, which was rapidly progressive and refractory to conventional therapies.

2. Case history

A 47-year-old lady was referred to our centre with an extensive ulcerating tumour on the anterior chest wall (Fig. 1). She had presented 3 years previously with an inflammatory cancer of the left breast and with clinically detectable adenopathy in the left axilla. Clinical and radiological investigation revealed no evidence of distant metastasis. Four cycles of neo-adjuvant Adriamycin and Cyclophosphamide had minimally down staged the tumour and a left mastectomy

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Fig. 1 – Local chest wall recurrence of inflammatory breast cancer, unresponsive to systemic chemotherapy.

Fig. 2 – Thirty months following initial presentation: the ulcer has decreased in size dramatically as a result of large areas of re-epithelialisation and the patient is symptomatically well. Arrow indicates area of local reactivation of tumour which is decreasing in response to treatment.

and axillary clearance was performed. Histology of the tumour showed a 6 cm high grade papillary adenocarcinoma with positive nodes in all three levels of the axillary dissection and significant vascular invasion. The tumour was found to be ER/PR negative but HER2 positive. Postoperatively the patient received four cycles of Taxol and local field radiation therapy.

Four months later some inflammatory changes were noted at the lateral end of the scar. Biopsy confirmed tumour recurrence for which Navelbine, Taxotere and Herceptin were commenced. The tumour progressed, requiring daily dressings, and a course of 6 cycles of Gemcitabine was initiated. Spreading inflammatory changes in the right breast were treated with external beam radiotherapy. A computerised tomography (CT) scan at this time revealed pulmonary metastases but no other systemic disease. The tumour on the left chest wall was by now a 4.5×5 cm, ulcerating lesion and clearly refractory to conventional therapy (Fig. 1) which was withdrawn and the patient referred to our service for treatment with electrochemotherapy.

Under intra-venous sedation the patient received 20,000IU of bleomycin intravenously and 5000IU intra-tumourally. Eight minutes after the intra-venous bolus, a consecutive series of electric pulses (1400 V/cm intensity, 100 μs duration) were delivered to the tumour across intra-tumourally placed linear array needle electrodes. The electrodes were repositioned until the entire tumour was treated. The patient received three such treatments over a 7-month period all of which were administered in an out-patient setting. The first two resulted in minimal reduction in tumour volume, with subsequent progression. However, following the third treatment, a dramatic reduction in the tumour mass was accompanied by relief of the pain and bleeding, culminating in a complete elimination of tumour on the chest wall. Due to this response systemic chemotherapy was recommenced with 10 cycles of CMF. The remaining ulcer was seen to contract over time with re-epithelialisation at the periphery (Fig. 2). CT scanning demonstrated quiescence of the pulmonary lesions and the chest wall remained tumour-free for ten months. A subsequent small local recurrence 30 months later has responded well to further electrochemotherapy and the patient remains symptomatically well and has declined consideration for skin graft of the residual ulcer.

3. Discussion

This report demonstrates that multiple applications of electrochemotherapy can induce a remission in a locally destructive breast cancer recurrence, which was refractory to multimodal therapy. Moreover, electrochemotherapy is advantageous to patient care as hitherto conventional treatments including surgical intervention and less invasive oncology choices are limited in their ability to effectively localise treatment to cancerous tissues without causing disruption to non-target physiological tissues, functions and organs.[2] Because of its therapeutic efficacy and minimal side effects electrochemotherapy could with benefit be applied earlier in the clinical course of locally recurrent cancers and would be tolerated when used in combination with standard systemic agents. It is noteworthy that tumours respond to electrochemotherapy even when resistant to conventional regimens and when recurrent after previous electrochemotherapy.

Extensive chest wall recurrences are rarely suitable for excision and chest wall reconstruction. Colonisation of the ulcers by bacteria and radiation injury to the surrounding tissues predispose the patient to wound infection and failure after surgery. While some of these problems can be overcome by reconstructing with free transfer grafts because of the scale of the surgery and the protracted duration of convalescence the cancer has often recurred prior to rehabilitation of the pa-

tient. These cancers permeate the dermal lymphatics and are prone to recur at variable periods after excision so multiple interval therapies are warranted and extensive excision is rarely curative. Electrochemotherapy has been established as an effective means of treating tumours that present as primary and secondary cutaneous, sub-cutaneous and local recurrences which prove to be refractory to conventional treatment. Diverse tumour types which are responsive to electrochemotherapy include metastatic malignant melanoma, squamous cell carcinoma, basal cell carcinoma and recurrent breast adenocarcinoma.[3–5] Electrochemotherapy is ideally suited to multiple applications and the cumulative dose of bleomycin would rarely approach levels associated with side effects or toxicity. Our experience with this patient was very gratifying where multiple applications of electrochemotherapy, applied during out-patient visits, resulted in tumour regression and an immediate improvement in quality of life.

Current limitations of this treatment include its restricted suitability for cutaneous and subcutaneous tumours, however, a myriad of unresectable symptomatic cancers could benefit from the development of new electrodes and operating procedures. The development of such technology capable of delivering permeabilising electric pulses to intraluminal gastrointestinal or urinary tract tumours endoscopically, or to intra-abdominal tumours via the laparoscopic approach may ensure that a great many tumours which are now deemed inoperable or are unresponsive to conventional therapy would then be accessible to electrochemotherapy. Tumour burden reduction or tumour regression would be a feasible aim, facilitating the achievement of palliation of symptoms, improvement of quality of life, prolongation of survival and perhaps cure.[6] Moreover, the role, this technology may play in the delivery of immunologically active impermeant molecules or cytokines to tumours is an exciting area of current research. The manifold benefits possible from the introduction of such therapies may allow for the development of innate immunological protection against the development of metastatic disease and as such would represent a therapeutic advance.[7]

4. Conclusion

Electrochemotherapy induced a clinically significant remission of a progressive and destructive chest wall recurrence of a breast cancer which was refractory to multimodal therapies. A delayed tumour recurrence at 30 months was again responsive to the electrochemotherapy. Tumour regression was accompanied by a dramatic improvement in quality of life. This experience in aggressive refractory cancer suggests that electrochemotherapy techniques should be developed for more widespread clinical usage.

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